

sive data to confirm this. Frequency of diagnosis of milder cases is likely a major factor in determining the mortality. Although the mortality may be decreasing, the decrease is not significant,¹ despite dramatic improvements in therapy of the disorder. This raises important questions about the true value of the therapeutic modalities developed in recent years and accepted as being valuable.

Pathology of ARDS

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IN THE MIDDLE 1960's when ARDS was emerging as a clinical entity, pathologists were impressed with unusual gross and microscopic appearances of the lungs of patients who had died as a result of the syndrome. In 1967 Drs. Nash, Blennerhassett and Pontoppidan¹¹ reported on an autopsy study of patients (many with ARDS) who had died in a respiratory intensive care unit. In that study, the lungs of those patients were compared with those of patients in a control autopsy population who had not had acute respiratory failure and who had never been treated with a mechanical ventilator. A wide range of gross and microscopic changes were encountered with approximately equal frequency in the two groups. However, two distinctive lesions were found in the study group that set this group apart from the control population.

The first lesion was characterized grossly by heavy consolidated lungs that had a homogeneous beefy-red appearance. Only a small amount of serosanguineous fluid could be scraped from the cut surface; the foamy pink fluid, characteristic of intraalveolar edema, was not present. Microscopically, such lungs showed capillary congestion, marked interstitial edema, a moderate amount of intraalveolar fibrinous exudate and focal alveolar hemorrhage. The most striking finding, and one which typified this lesion, was the presence of hyaline membranes lining alveolar ducts, alveoli and some respiratory bronchioles.

The second lesion, which separated the study group from the control population, was a pattern of early interstitial fibrosis found in many patients who had died in the respiratory unit. Viewed grossly, the lungs of these patients were charac-

terized by a greyish-pink consolidation without demonstrable exudate, suggesting a degree of fibrous organization. On microscopic examination, there was pronounced interstitial thickening with a combination of edema fluid, histiocytes, fibroblasts, increased reticulin and collagen fibers. The normal alveolar surface had been replaced by large rounded or cuboidal cells, a finding commonly referred to as "hyperplasia of alveolar lining cells" by pathologists. Some lungs in the patients of the study group showed a combination of the two distinctive patterns, with evidence of hyaline membranes undergoing organization and early interstitial fibrosis.

When the pathologic changes were correlated with the duration of ARDS, it became apparent that the two distinctive lesions, which characterized the lungs of the patients in the study group, were really phases in the evolution of a particular type of morphologic response of the lung to injury. In general, patients with ARDS who died after a week or less had the interstitial edema-hyaline membrane pattern. Those who lived two weeks or more had the early interstitial fibrosis pattern, and patients who died after one to two weeks had a combination of the two patterns. The interstitial edema-hyaline membrane lesion was called the exudative phase and the early interstitial fibrosis picture was the proliferative phase of the process.

A closer look at the clinical information available on the study group patients showed that patients with the exudative or proliferative lesions had been treated with toxic concentrations of oxygen for prolonged periods. We concluded that the lesions probably represented phases in the evolution of pulmonary oxygen toxicity in man. Additional studies by other investigators on similar patients with ARDS showed comparable findings and also implicated oxygen toxicity as the likely cause of the lesions.¹²⁻¹⁵ Furthermore, the findings in experimental studies showed that the exudative and proliferative lesions described in patients with ARDS could be reproduced in animals by exposing them to toxic concentrations of oxygen for prolonged periods.¹⁶⁻¹⁹

These studies led to a judicious use of oxygen in the treatment of acute respiratory failure, with an attempt to avoid administering toxic levels unless absolutely necessary to maintain life. In the new enlightened era of oxygen therapy, some patients died with complications of ARDS who had never required and therefore never received toxic concentrations of oxygen. When their lungs were

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examined at autopsy, the same exudative and proliferative lesions characteristic of oxygen toxicity were found. The reason for this is that the morphologic changes seen in ARDS represent a non-specific reaction of the lung to various deleterious agents.²⁰ Although these changes are characteristic of pulmonary oxygen toxicity, they are also seen in radiation pneumonitis and influenza pneumonia, and after the inhalation of chlorine, phosgene, carbon dioxide at high tensions and mercury vapor. Ingestion of kerosene and paraquat has been associated with these changes, as have toxic reactions to various drugs including busulfan, bleomycin, cyclophosphamide, melphalan, hexamethonium, nitrofurantoin and methysergide. In addition to specific agents causing this reaction, several conditions are associated with it, including hyaline membrane disease of the newborn, and the group of conditions encompassed by the term ARDS such as shock, trauma, drug coma and sepsis. The name that has been adopted for this reaction is diffuse alveolar damage (DAD).

The development of DAD at the ultrastructural level has been well documented in pulmonary oxygen toxicity, both in experimental animals and in man.^{17,21-25} Although DAD not associated with oxygen toxicity in patients with ARDS has not been as thoroughly studied, the evidence that does exist suggests a similar sequence of morphologic alterations.^{26,27} The first change that occurs in pulmonary oxygen toxicity is the development of interstitial edema, usually within 48 hours of breathing 100 percent oxygen in most species. At this time there may not be evidence of damage to the alveolar capillary endothelium that could account for a change in capillary permeability; this condition cannot be differentiated from hemodynamic pulmonary edema on a morphologic basis.^{21,28,29} However, with continued exposure to toxic concentrations of oxygen (about three to seven days) profound changes occur in the alveolar epithelium and endothelium of alveolar capillaries, with evidence of injury followed by necrosis and eventual sloughing of the cells from their basement membranes. Fibrin-platelet thrombi may develop in the capillaries denuded of endothelium, resulting in exudation of fluid, plasma proteins and some erythrocytes into the interstitial and alveolar spaces. The necrotic alveolar epithelium, mainly type I pneumocytes, plus fibrin and other plasma proteins make up the hyaline membranes characteristic of the exudative phase of DAD. At this stage the lesion clearly differs from hemodynamic

pulmonary edema, which is not associated with diffuse necrosis of the cells of the air-blood membrane.^{28,29} After necrosis the capillary endothelium and alveolar epithelium regenerate, a process that may be completed in a few days.^{17,25,27,30} The cell that is responsible for repopulating the alveolar surface is the type II cell or granular pneumonocyte, the same cell that secretes surfactant.^{17,25,27} Granular pneumonocytes vary from large rounded to cuboidal cells. Consequently, when they cover the entire alveolar surface, the alveolar epithelium seems hypertrophied and hyperplastic. While regeneration of epithelium and endothelium takes place, many fibroblasts and collagen fibers become apparent in the interstitium.^{17,25,27} These changes constitute the ultrastructural counterpart of the proliferative phase of DAD as seen by light microscopy.

As a common nonspecific reaction of the lung to injury, DAD is not a diagnosis nor does it imply anything about causes. When DAD is found in a patient, it should prompt a careful search of the clinical data for a possible cause. Oxygen toxicity was probably a major cause of ARDS in the days when toxic concentrations of oxygen were administered almost routinely to patients in whom mechanical ventilation was required. Even today, it undoubtedly contributes to the development of DAD in some patients with ARDS. However, there are many patients who die of ARDS in whom the cause of DAD remains unknown.

An important question that confronts pathologists and clinicians today is the natural history of DAD. Diffuse alveolar damage was the lesion seen in the early phase of the Hamman-Rich syndrome, and it probably is an important precursor of idiopathic interstitial fibrosis.³¹ Does DAD invariably lead to interstitial fibrosis or can it resolve with little or no residuum? This question has considerable practical significance in ARDS because the technology is available to prolong the lives of patients, either with conventional ventilatory care or with extracorporeal oxygenation. Examination of the lungs of patients dying after prolonged therapy for ARDS has shown that a striking degree of pulmonary fibrosis can develop in a few weeks, rather than months or years as was previously believed.^{32,33} Alternatively, some patients with ARDS have prolonged clinical courses and recover completely. Presumably, these persons had significant pulmonary changes that resolved. It is generally believed that the exudative phase of DAD is potentially reversible and a well-devel-

oped proliferative lesion is not compatible with resolution.³² However, a recent study by Koeniger³⁴ has cast doubt on this concept. In this study lung biopsy studies were done on patients with ARDS who eventually survived with little or no functional impairment. Findings in these studies were similar to those in biopsy studies from patients who did not survive, with some biopsy specimens from each group showing a well-developed proliferative phase of DAD. This study has shown that survival is possible with extensive lung damage and that the finding of the proliferative phase of DAD in a lung biopsy study does not necessarily mean that the prognosis is hopeless. However, a disturbing conclusion of this work is that, at present, morphologic criteria do not exist that would enable a pathologist to predict the outcome of ARDS from a biopsy study showing DAD. It is hoped that this situation will change as more data from studies involving sequential lung biopsy studies become available.

Lung Vascular Permeability and Primary Pulmonary Edema

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STUDIES BY Guyton and Lindsey³⁵ suggest that the lung is normally dry because the plasma oncotic pressure (absorption force) exceeds the microvascular hydrostatic pressure (filtration force).³⁵ Alveoli are normally dry, but the lung as a whole contains much water.³⁶ The mechanisms for keeping alveoli dry are more complicated than originally believed.³⁶⁻³⁸

What Keeps Alveoli Dry?

Lung Lymph Flow

Under normal conditions lymph flows from the lung; this indicates that the net Starling forces are normally favoring filtration in the lung as in all other organs. When hydrostatic pressure is increased in exchanging vessels, lymph flow increases even at pressures too low to cause edema (Figure 1).^{36,39,40} Therefore, when filtration is increased, lymph flow increases (about double for a 15 cm of water microvascular pressure increase) and this prevents fluid from accumulating in the lung.

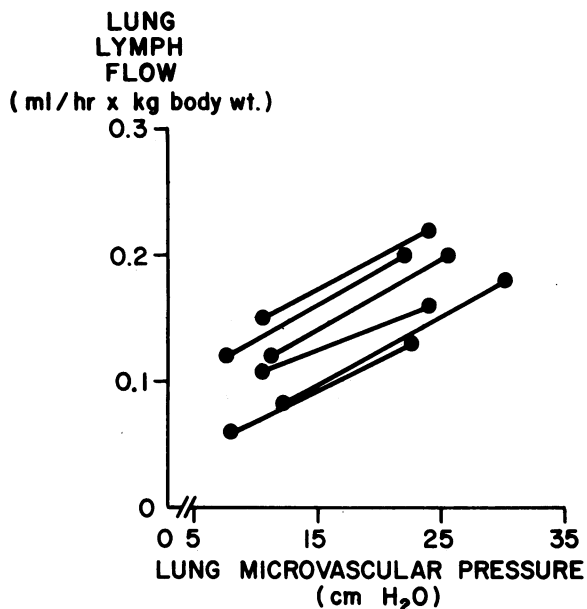


Figure 1.—Effects of mechanically increased lung vascular pressure (left atrial balloon inflation) on lung lymph flow in awake sheep. Microvascular pressure is left atrial pressure plus 0.4 (pulmonary artery pressure minus left atrial pressure). Moderate pressure increases cause lymph flow to increase. Lymph flow doubles for a 15 cm of water microvascular pressure increase.

Interstitial Oncotic Pressure

All of the small molecules in plasma equilibrate with the interstitial space so that the main solutes exerting osmotic forces across exchanging vessel walls are proteins. In the lung, effective interstitial (lymph) protein concentration is normally high (about two thirds of the plasma concentration).³⁶⁻⁴¹ If interstitial protein concentration could fall relative to plasma, this would increase the osmotic force favoring absorption and thereby help protect against excessive filtration and edema. Figure 2 shows what happens when hydrostatic pressure is increased in lung vessels: lymph flow goes up and lymph protein concentration goes down.³⁶

There is nothing miraculous about the fall in filtrate protein with increasing filtration rate; that is exactly how a semipermeable membrane ought to behave.⁴² Because water moves freely across the membrane and proteins are restricted, increased pressure causes a relatively larger increase in water flux. As lymphatics drain the filtrate away from the interstitial space, a "wash-down" of interstitial protein concentration occurs.^{36,42} Consequently, the decrease in interstitial oncotic pressure is a negative feedback that normally off-

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